Journal of the American College of Cardiology
© 2002 by the American College of Cardiology Foundation
Published by Elsevier Science Inc.

Vol. 40, No. 6, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(02)02119-8

Prospective Analysis of Creatine Kinase Muscle-Brain Fraction and Comparison With Troponin T to Predict Cardiac Risk and Benefit of an Invasive Strategy in Patients With Non–ST-Elevation Acute Coronary Syndromes

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OBJECTIVES We sought to determine whether elevation of plasma creatine kinase muscle-brain fraction (CK-MB) would be useful to triage patients with acute coronary syndromes (ACS) to early angiography/revascularization.

BACKGROUND It is unknown whether the measurement of CK-MB is effective for triage to an aggressive management strategy.

METHODS Patients in the Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy (TACTICS-TIMI) 18 study received aspirin, heparin, and tirofiban for treatment of ACS, were randomized to an invasive or a conservative strategy (angiography/revascularization between 4 and 48 h), and were followed up for a composite end point of death, myocardial infarction, or rehospitalization for ACS.

RESULTS Of 2,220 patients, CK-MB was elevated in 826 (37%). Of the patients with negative CK-MB, troponin T was elevated in 361 (31.2%). Event rates at 30 and 180 days were twice as high in patients with elevated CK-MB than in patients without elevated CK-MB. Both groups had similar benefit from an invasive strategy; there was no evidence of interaction between CK-MB elevation and strategy on the composite end point at 30 or 180 days. When patients were stratified according to both CK-MB and troponin status, there was evidence of a benefit in the invasive strategy among patients who were CK-negative but troponin-positive (odds ratios [95% confidence interval]: 0.13 [0.04 to 0.39] at 30 days and 0.29 [0.16 to 0.52] at 180 days).

CONCLUSIONS Patients with minimal amounts of recent onset myonecrosis but elevated risk as indicated by CK-MB and troponin, respectively, benefit most from invasive management. Determination of troponin levels yielded significant information regarding triage to an invasive strategy, particularly in CK-MB-negative patients. (J Am Coll Cardiol 2002;40:1044–50) © 2002 by the American College of Cardiology Foundation

Non-ST-segment elevation acute coronary syndromes (ACS) account for more than 1,420,000 hospitalizations in the U.S. (1). The pathophysiology in most cases centers about plaque rupture, critical coronary arterial narrowing, and intravascular thrombosis. A management strategy characterized by treatment with either a low molecular weight heparin or a platelet glycoprotein IIb/IIIa antagonist followed by angiography and revascularization can reduce the likelihood of subsequent recurrent angina, myocardial infarction (MI), and mortality (2,3). Given the large number of patients who present with ACS, such an approach has two major limitations. First, it requires performing coronary angiography and percutaneous coronary intervention (PCI) or coronary artery bypass surgery in high-risk as well as low-risk patients who may not stand to benefit from this approach. Second, it is resource-intensive and often requires patient transfer to institutions with the facilities to perform these procedures.

A variety of instruments have been proposed to stratify patients with ACS according to risk and to the likelihood of benefiting from an aggressive invasive strategy. Use of serum biomarkers, indicating the presence of myocardial necrosis, has been proposed as a useful strategy to triage patients to an invasive or noninvasive management plan. In the Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy (TACTICS-TIMI) 18 study, a prospective substudy indicated a significant interaction between the presence of troponin T levels >0.01 ng/ml and an aggressive management strategy (3,4). A recent consensus conference indicated that troponin was the "preferred" marker for the diagnosis of MI (5). In comparison with troponin determinations, measurement of creatine kinase muscle-brain fraction (CK-MB) is more universally available and, in many cases, less expensive to perform. Levels of the isoforms of this enzyme, and perhaps

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Manuscript received December 18, 2001; revised manuscript received May 29, 2002, accepted June 19, 2002.

Abbreviations and Acronyms

ACS	= acute coronary syndromes
CAD	= coronary artery disease
CK	= creatine kinase
CK-MB	= creatine kinase muscle-brain fraction
GUSTO	= Global Utilization of Strategies to Open Occluded Coronary Arteries
MI	= myocardial infarction
OR	= odds ratio
PCI	= percutaneous coronary intervention
TACTICS-TIMI	= Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy

the total concentration of the enzyme, also become elevated at an earlier stage than serum troponin (6). Consequently, measurement of CK-MB may be useful at an early stage in the evaluation of patients with ACS to decide whether rapid triage to coronary angiography or a more conservative approach is indicated. We prospectively assessed the TACTICS-TIMI 18 study to test the hypothesis that measurement of CK-MB could discriminate between patients who did or did not benefit from an early invasive strategy.

METHODS

The methods and primary findings of TACTICS-TIMI 18 have been published (3). Patients presenting within the first 24 h of a chest pain syndrome believed to be ischemic and who had either a history of coronary artery disease (CAD) or an electrocardiographic ST-segment deviation, a T-wave inversion, or an elevation of the CK-MB or troponin were eligible. Patients were treated with aspirin 325 mg daily, heparin given as a 5,000 U intravenous bolus followed by an infusion at 1,000 U/h, and tirofiban given as a 0.4 μg/kg/min infusion for 30 min followed by 0.1 μg/kg/min. They were randomized to undergo either: 1) an early invasive management strategy characterized by angiography 4 to 48 h after randomization, followed by anatomically directed revascularization; or 2) a conservative strategy characterized by exercise treadmill testing and angiography for test results indicating either high risk or spontaneous recurrent ischemia. After PCI, tirofiban infusions were to be continued for the following 24 h.

At the time of randomization, blood samples were drawn every 8 h for the first 24 h and assayed locally. A sample drawn at enrollment was assayed at a core laboratory for creatine kinase (CK) and its MB fraction using the Bayer ACS:180 CK-MB assay. The coefficient of variation for CK-MB at this laboratory ranges between 5% and 7%. Troponin T was also measured in this sample (Elecsys 10/10, Roche Diagnostics, Indianapolis, Indiana). Enrollment MI was defined as an elevation in CK-MB above the upper limit of normal on a sample obtained during the 24 h before or after randomization, in the absence of a revascularization procedure. The admission core laboratory specimen was used for the determination of enrollment MI, but when a core laboratory value was not available, the site determination was used.

The primary end point of the study was a composite of death, MI, and rehospitalization for an ACS at six months. The composite of death and MI was a secondary end point. Myocardial infarction was determined as an increase in CK-MB exceeding twice the normal value at the enrolling site or the development of new Q-waves. Within 24 h after a PCI, MI was defined as a threefold increase in CK-MB.

Statistical methods. Continuous variables are represented as means and SDs; discrete variables are reported as median values and 25th and 75th percentiles. Inferential comparisons were made using chi-square tests for continuous discrete variables and appropriate parametric tests for continuous variables. Odds ratios (ORs) were calculated for event rates at 30 days and six months. Logistic regression was used to adjust ORs for baseline variables that were different between patients with and without MI at the time of enrollment. This adjustment is reported both before and after the addition of troponin T $\geq$0.01 ng/ml to the model.

RESULTS

Of the 2,220 patients enrolled in TACTICS-TIMI 18, core CK-MB values were available in 1,825 patients, and on-site CK-MB values were used in 395. The CK-MB was elevated in 826 (37%). This determination was based on core lab data in 534 (65%) patients found to have enrollment MI. Core lab troponin data were available in 1,825 patients. Of the 668 patients with elevated CK-MB who had troponin data available, 625 (94%) had troponin T values $\geq$0.01 ng/ml, while of the 1,157 patients without CK-MB elevation, 361 (31%) had troponin T values $\geq$0.01 ng/ml. The majority of enrollment infarctions were characterized by peak CK values $<3\times$ the upper limit of normal and by either ST-segment depression or elevation (Table 1). Patients with MI were more likely to be male or have a prior history of smoking but were less likely to have other established risk factors for CAD, to have been treated with an HMG Co-A reductase inhibitor, or to have undergone a coronary artery revascularization procedure (Table 1).

Among patients assigned to the invasive strategy, coronary angiography was performed in 98% of CK-MB-positive patients and 97% of CK-MB-negative patients (Table 2). Among patients assigned to a conservative strategy, 58% of patients with CK-MB elevation underwent angiography compared with 47% of patients with normal CK-MB ($p < 0.001$). Multivessel CAD was also more common in patients with CK-MB elevation. Regardless of the assigned treatment strategy, revascularization was performed more commonly in patients who were CK-MB-positive, regardless of the extent of disease discovered at

Table 1. Demographic Characteristics

	CK-MB +	CK-MB −	p Value
Weight (kg)	84.7 ± 17.9	83.3 ± 18.5	0.0768
Age (yrs)	62.1 ± 11.9	61.6 ± 11.5	0.2680
Male	73%, n = 606	62%, n = 857	<0.001
Diabetes	26%, n = 213	29%, n = 400	0.139
Smoker			
Current	35%, n = 286	29%, n = 392	0.002
Former (ever)	74%, n = 608	70%, n = 967	0.040
Hypertension	60%, n = 492	70%, n = 975	<0.001
Hyperlipidemic	55%, n = 453	64%, n = 893	<0.001
On a statin	19%, n = 154	28%, n = 390	<0.001
Prior MI	33%, n = 271	43%, n = 595	<0.001
Prior CABG	16%, n = 135	25%, n = 349	<0.001
Prior PCI	18%, n = 150	33%, n = 462	<0.001
On heparin before randomization	2%, n = 19	2%, n = 31	0.907
On aspirin before randomization	60%, n = 493	71%, n = 984	<0.001
ST elevation	16%, n = 128	9%, n = 126	<0.001
ST depression	36%, n = 299	27%, n = 378	<0.001
T-wave inversion only	16%, n = 133	24%, n = 329	<0.001
No ECG Δ	37%, n = 309	43%, n = 597	0.012
Troponin T ≥ 0.01 ng/ml	94%, n = 625	32%, n = 361	<0.001

CABG = coronary artery bypass grafting; CK-MB = muscle-brain fraction of creatine kinase; ECG = electrocardiogram; MI = myocardial infarction; PCI = percutaneous coronary intervention.

angiography (single-vessel disease 78% vs. 62%, $p < 0.001$; double-vessel disease 81% vs. 74%, $p = 0.08$; triple-vessel disease 76% vs. 72%, $p = 0.28$). However, once a revascularization procedure was undertaken, the procedure appeared to be performed similarly regardless of CK-MB status. Operator-reported success rates were also similar between the two groups (Table 2).

At both the 30-day and six-month points, the composite end point occurred more frequently in patients with CK-MB elevation (Tables 3 and 4, Figs. 1 and 2). For the primary composite, event rates were approximately 50% higher in this group, while for the composite of death or MI, they were approximately twice as high. Event rates also increased as the peak value of CK increased (data not shown).

Odds ratios for patients with, as well as for patients without, CK-MB elevation favored the invasive strategy at both 30 days and six months. After adjusting for differences in baseline variables, the ORs were even more favorable for both strategies, although, in patients without enrollment MI, the 95% confidence limits exceeded unity for both the double and triple composites at both time points (Table 4).

There was no evidence of statistical interaction between CK-MB status and assigned treatment strategy: $p = 0.37$ for the primary composite end point at 30 days and $p = 0.58$ at six months; $p = 0.28$ and 0.77 for the end point of death or MI at 30 days and six months, respectively. After adjustment for baseline characteristics, there was still no evidence for a difference in treatment effect according to elevation of the CK-MB ($p = 0.26$, 0.38, 0.18, and 0.38, respectively). When patients were stratified into tertiles of CK elevation, the ORs favoring a benefit of the invasive strategy on the primary composite end point at 30 days were 0.83 (95% confidence interval [CI], 0.25 to 2.78, $p = 0.76$), 0.75 (95% CI, 0.20 to 2.76, $p = 0.66$), and 1.05 (95% CI, 0.30 to 3.69, $p = 0.94$) for the first through third tertiles, respectively. At 180 days the respective ORs were 0.92 (95% CI, 0.35 to 2.41, $p = 0.86$), 0.95 (95% CI, 0.34 to 2.66, $p = 0.92$), and 0.45 (0.17 to 1.21, $p = 0.12$).

Stratification of patients according to both CK-MB and troponin at the time of study enrollment (Table 5) indicated that determination of both values yielded important infor-

Table 2. Procedural Details

	Invasive			Conservative		
	CK-MB +	CK-MB −	p Value	CK-MB +	CK-MB −	p Value
Duration of tirofiban (h)	48.4	48.1	0.0012	52.1	49.1	0.068
(median 25th/75th %)	(47.3, 62.5)	(38.3, 55.4)		(48, 68.5)	(48, 69.6)	
Angiogram performed	98%	97%	0.471	58%	47%	< 0.001
# of vessels diseased			< 0.001			0.007
0	7.4%	17%		4.7%	12%	
1	26%	25%		26%	28%	
2	31%	26%		31%	23%	
3	36%	32%		38%	36%	
LMCA	8.3%	8.6%	0.893	11%	9.9%	0.54
Any revascularization	71%	54%	< 0.001	44%	32%	< 0.001
PCI performed	51%	35%	< 0.001	32%	21%	< 0.001
Stent placed	84%	80%, 198/247	0.334	88%	85%	0.49
Number of vessels attempted	1.1 ± 0.58	1 ± 0.49	0.1314	1.1 ± 0.52	1.1 ± 0.53	0.20
Duration of tirofiban after PCI in days (median 25th/75th %)	0.97 (0.55, 1.3)	1.03 (0.57, 1.35)	0.1294	0 (0, 0.56)	0.01 (0, 0.65)	0.24
PCI success	92%	96%	0.045	95%	95%	0.81
2nd PCI performed	4.7%	4.1%	0.743	4.6%	6.2%	0.56
CABG performed	21%	19%	0.507	15%	12%	0.11
# of grafts placed	31 ± 0.9, n = 87	2.9 ± 0.99	0.1933	31 ± 0.95	3.0 ± 0.99	0.55

CABG = coronary artery bypass grafting; CK-MB = muscle-brain fraction of creatine kinase; LMCA = left main coronary artery; PCI = percutaneous coronary intervention.

Table 3. Cardiac Events at 30 and 180 Days

	A. Individual Event Rates at 30 Days					
	CK-MB + (n = 826)			CK-MB − (n = 1,394)		
	Inv.	Cons.	p Value	Inv.	p Value	p Value
Death	13 (3.1%)	11 (2.7%)	0.7	12 (1.7%)	7 (1.0%)	0.24
Myocardial infarction	16 (3.8%)	36 (8.8%)	0.003	18 (2.6%)	28 (4.0%)	0.13
Rehospitalization for angina	19 (4.6%)	33 (8.1%)	0.038	19 (2.7%)	28 (4.0%)	0.18
	B. Individual Event Rates at 180 Days					
	CK-MB + (n = 826)			CK-MB − (n = 1,394)		
	Inv.	Cons.	p Value	Inv.	p Value	p Value
Death	19 (4.6%)	21 (4.1%)	0.7	18 (2.6%)	18 (2.6%)	1.0
Myocardial infarction	28 (6.7%)	41 (8.8%)	0.09	25 (3.6%)	35 (5.0%)	0.19
Rehospitalization for angina	49 (11.8%)	63 (15.4%)	0.13	74 (10.6%)	89 (12.8%)	0.18

CK-MB = muscle-brain fraction of creatine kinase; Cons. = conservative; Inv. = invasive.

mation. When both markers were negative, there was almost no benefit to an invasive strategy; when both were positive, the benefit appeared to be modest. By far, the greatest benefit was observed in patients with negative CK-MB but positive troponin T (ORs, 0.13 to 0.33). Univariate logistic regression analysis confirmed highly significant interactions between CK-MB-negative but troponin-positive status and the composite end point. At 30 days the OR for the benefit of invasive versus conservative management was 0.13 (95% CI, 0.05 to 0.40, $p < 0.001$), and at 180 days it was 0.24 (95% CI, 0.12 to 0.50, $p < 0.001$).

DISCUSSION

Both clinical and economic considerations favor the development of improved triage strategies to select patients who are most likely to benefit from invasive management strategies. Measurement of CK-MB is an established technique for diagnosing MI, and CK-MB might be considered a likely candidate biomarker for development of a triage strategy. Although most index infarctions within TACTICS-TIMI 18 were relatively small, we nonetheless observed that rates of recurrent ischemic events during the first six months after presentation were 50% to 100% higher among patients with elevations of CK-MB. Despite a nearly

Table 4. Odds Ratios for Invasive and Conservative Management According to the Presence of Enrollment MI

	A. Unadjusted OR					
	CK-MB −			CK-MB +		
	OR for Inv. vs. Cons. Rx	95% CI	p Value	OR for Inv. vs. Cons. Rx	95% CI	p Value
30-day death/MI	0.82	0.48, 1.39	0.43	0.52	0.31, 0.87	0.015
30-day composite	0.85	0.55, 1.29	0.24	0.54	0.35, 0.82	0.012
6-month death/MI	0.76	0.49, 1.17	0.27	0.72	0.47, 1.11	0.109
6-month composite	0.90	0.67, 1.21	0.21	0.76	0.47, 0.93	0.053
	B. OR Adjusted for Baseline Characteristics					
	CK-MB −			CK-MB +		
	OR for Inv. vs. Cons. Rx	95% CI	p Value	OR for Inv. vs. Cons. Rx	95% CI	p Value
30-day death/MI	0.78	0.45, 1.33	0.353	0.50	0.29, 0.85	0.010
30-day composite	0.77	0.50, 1.18	0.231	0.55	0.35, 0.85	0.007
6-month death/MI	0.78	0.50, 1.22	0.270	0.65	0.42, 1.02	0.060
6-month composite	0.82	0.61, 1.11	0.203	0.68	0.48, 0.96	0.029
	C. OR Adjusted for Baseline Characteristics Including Troponin Elevations					
	CK-MB −			CK-MB +		
	OR for Inv. vs. Cons. Rx	95% CI	p Value	OR for Inv. vs. Cons. Rx	95% CI	p Value
30-day death/MI	0.63	0.34, 1.18	0.147	0.45	0.25, 0.83	0.010
30-day composite	0.64	0.40, 1.03	0.065	0.49	0.30, 0.80	0.004
6-month death/MI	0.70	0.42, 1.17	0.173	0.70	0.42, 1.17	0.173
6-month composite	0.79	0.57, 1.10	0.158	0.63	0.42, 0.94	0.022

CI = confidence interval; CK-MB = muscle-brain fraction of creatine kinase; Cons. = conservative; Inv. = invasive; MI = myocardial infarction; OR = odds ratio.

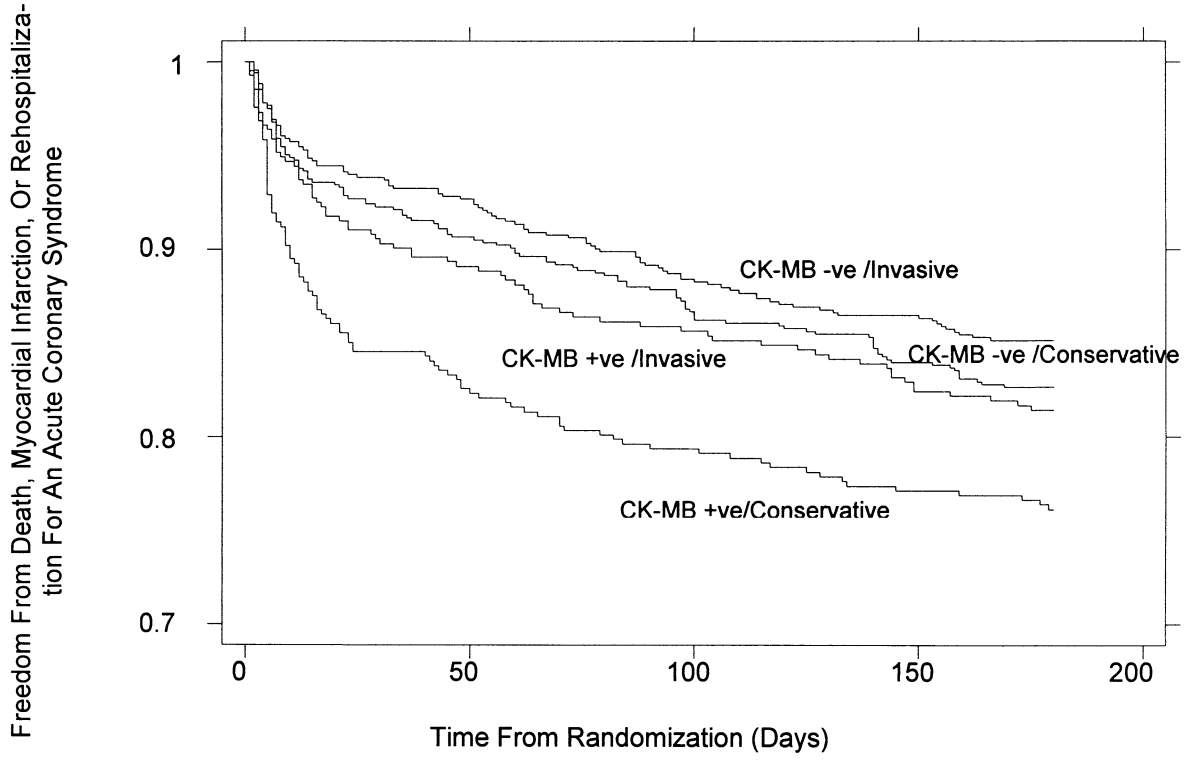

Figure 1. Kaplan-Meier estimates of survival free of the composite end point according to creatine kinase muscle-brain fraction (CK-MB) status and assignment to an invasive or conservative strategy.

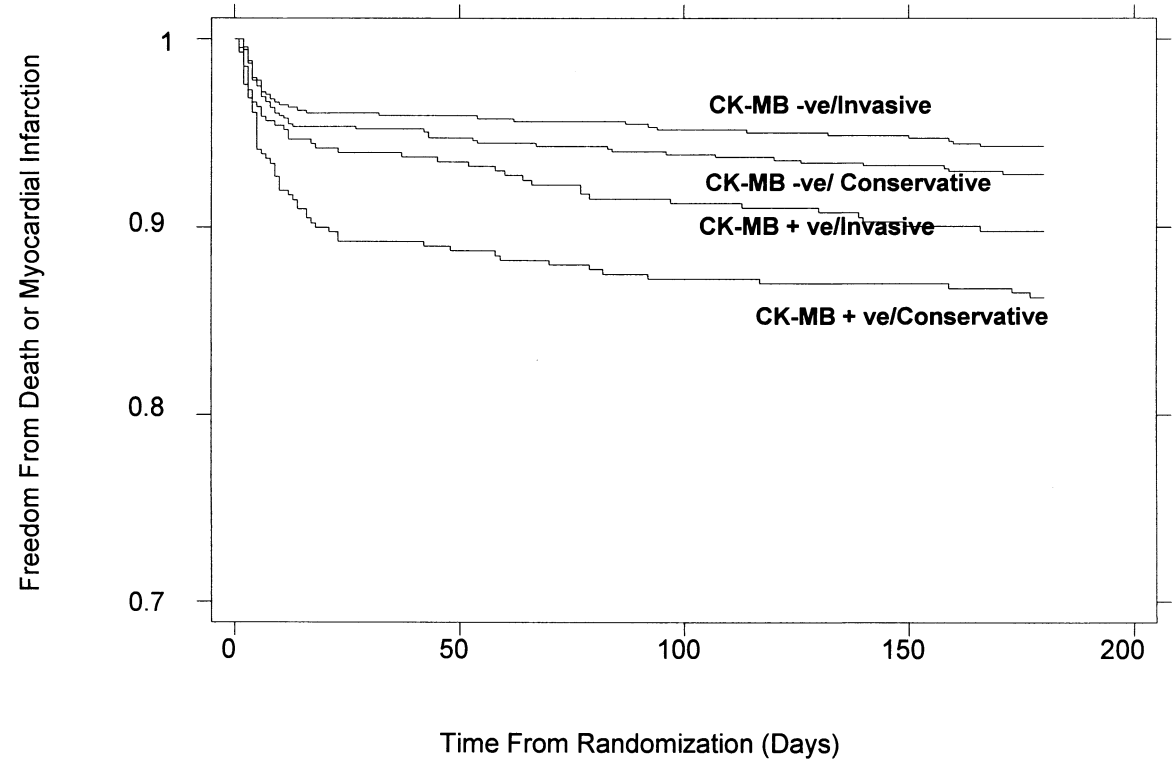

Figure 2. Kaplan-Meier estimates of survival free of death or myocardial infarction according to creatine kinase muscle-brain fraction (CK-MB) status and assignment to an invasive or conservative strategy.

Table 5. Logistic Regression (Univariate) for Death/MI and Composite End Point Stratified According to CK Elevation and Troponin Status

	Event Rate Inv.	Event Rate Cons.	OR for Inv. vs. Cons. Rx	95% CI	p Value
CK-/troponin − (n = 662)					
30-day death/MI (n = 20)	3.0%	3.1%	0.97	0.40, 2.36	0.945
30-day composite (n = 41)	6.0%	6.4%	0.92	0.49, 1.73	0.794
180-day death/MI (n = 32)	4.5%	5.2%	0.85	0.42, 1.73	0.653
180-day composite (n = 107)	17.3%	15.0%	1.18	0.78, 1.79	0.436
CK-/troponin + (n = 383)					
30-day death/MI (n = 28)	2.0%	13.3%	0.13	0.04, 0.39	< 0.001
30-day composite (n = 42)	3.0%	19.9%	0.12	0.05, 0.30	< 0.001
180-day death/MI (n = 35)	5.0%	13.8%	0.325	0.15, 0.70	0.004
180-day composite (n = 61)	8.4%	24.3%	0.29	0.16, 0.52	< 0.001
CK+/troponin − (n = 123)					
30-day death/MI (n = 3)	0%	4.3%	—	—	—
30-day composite (n = 6)	5.7%	4.3%	1.34	0.26, 6.92	0.727
180-day death/MI (n = 5)	1.9%	5.7%	0.32	0.03, 2.93	0.311
180-day composite (n = 19)	13.2%	17.1%	0.74	0.27, 2.02	0.551
CK+/troponin + (n = 559)					
30-day death/MI (n = 45)	7.0%	9.2%	0.75	0.40, 1.38	0.348
30-day composite (n = 70)	10.8%	14.3%	0.73	0.44, 1.21	0.220
180-day death/MI (n = 63)	11.2%	11.4%	0.98	0.58, 1.66	0.950
180-day composite (n = 119)	19.2%	23.4%	0.78	0.52, 1.17	0.225

CI = confidence interval; CK = creatine kinase; Cons. = conservative; Inv. = invasive; MI = myocardial infarction; OR = odds ratio.

50% reduction in the composite ischemic primary end point at 30 days among CK-MB-positive patients assigned to the invasive strategy, we did not observe statistical evidence that at six months the benefit of the invasive strategy was greater for these patients. Patients with, as well as without, elevated levels of CK-MB appeared to benefit from assignment to an invasive management strategy. Odds ratios were less than unity for both groups, although there was a weak trend toward an interaction at 30 days. Although event rates seemed to increase with increases in the peak CK value, we did not observe a parallel increase in the benefit of the invasive strategy. In contrast, our previously published findings using the troponin T assay indicated significant differences in benefit at 30 days and six months and progressive increases in this benefit with decreasing levels of troponin. Interaction terms for positive versus negative troponin at the 30-day and six month points were 0.013 and 0.003, respectively (3).

Several features of the current study may help explain these observations. First, although the group with positive biomarkers is event-rich and is highly likely to have significant CAD, a recent period of prolonged occlusion of a coronary artery is required to cause myonecrosis. We chose to examine CK-MB in this study because histological studies have linked it unequivocally to myocardial necrosis (7,8) and because it is released rapidly after cell death. The ability of plasma CK-MB, and particularly its isoforms, to rise quickly after the onset of cell death is useful in diagnosing MI and reinfarction. In a recent multicenter study of patients with MI, values of CK-MB mass were elevated in 16% and 39% of patients at 2 and 4 h, respectively, after the onset of chest pain, compared with 10% and 37% for troponin T (6), whereas in another single-center study, the sensitivity at 3 h for CK-MB mass >5 μg/l was 47%, while that for troponin T >0.06 mg/l was 20% (9).

Relationship between CK-MB and troponin. Although, by definition, patients in the current study without CK-MB elevation did not have traditional evidence of recent myonecrosis, 31% had elevation of troponin T. An interesting observation was that this group appeared to have an amplified benefit from the invasive strategy. Although the exact magnitude of this finding cannot be firmly established in a relatively small number of patients (383), it does provide evidence of the heterogeneity of patients without CK-MB elevation. While the ORs for patients who had elevation of neither enzyme were close to unity, those who had evidence of troponin elevation despite negative CK-MB had ORs <0.33. Early investigations suggested that, because of its relatively small size and presence in the myocardial cytosol, troponin T might be an indicator of myocardial ischemia rather than cell death (10). However, the relationship between troponin release and the presence of necrosis has not yet been established. It is possible that patients in this latter group had transient reversible ischemia or that they had more temporally remote myocardial necrosis with subsequent recovery and a greater quantity of viable myocardium, which was protected by a revascularization strategy. This analysis represents a relatively small subgroup within the study and, as such, should be regarded as hypothesis-generating. If confirmed in subsequent studies, these data suggest that a dual marker triage strategy might ultimately be useful for patient triage and that abandonment of

CK-MB determination in favor of troponin alone may be premature.

Implications for early triage. The TACTICS-TIMI 18 study did not examine the effects of an immediate revascularization strategy on clinical outcomes. Rather, the invasive strategy relied on "upstream" anti-platelet therapy and was, by intent, designed to test invasive management after a minimum of 4 h of pharmacologic quiescence of an ACS. In patients with ACS, the majority of recurrent events consist of reinfarction and recurrent ischemia rather than the sequelae of ventricular dysfunction, as is seen in patients with ST-segment-elevation infarction (11,12). An analysis of patients enrolled in the Global Utilization of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb study indicated that the "front-loading" of events within the first 24 h previously observed in patients with ST-segment-elevation infarction is not present in patients with non-ST-segment ACS (13). For the purpose of assessing a strategy designed to manage longer-term sequelae of ACS, a biomarker that has a longer plasma half-life would be expected to be a better discriminator of patients who have high-risk coronary arterial lesions. Biomarkers that are released and cleared rapidly, such as CK-MB or its isoforms, may prove to be more useful discriminators in studies evaluating mechanical reperfusion strategies in the first few hours after presentation of patients with non-ST-segment elevation ACS.

Acknowledgment

We thank Dr. Robert Roberts for his thoughtful insights into the construction of this manuscript.

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